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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
KERR, J	
ART UNIT	PAPER NUMBER
1633	14

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/913,918	Applicant(s) Prockop et al.
	Examiner Janet M. Kerr	Group Art Unit 1633

☒ Responsive to communication(s) filed on *Sep 15, 1999* .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-68* is/are pending in the application.

Of the above, claim(s) *1-36 and 39-54* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *37, 38, and 55-68* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *6*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

The Information Disclosure Statement, filed on 9/14/98, has been entered.

Applicant's election of Group V, in Paper No. 10, filed on 6/1/99, and the election of the obesity factor species in Paper No. 13, filed on 9/15/99 are acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirements, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-68 are pending.

Claims 1-36, and 39-54 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention.

Claims 37, 38, 55, and 57-68 are being examined on the merits, and 56 is being examined as it relates to the elected species, obesity factor.

Specification

The specification is objected to because the priority data does not appear in the first paragraph of the specification. Specifically, after the title on page 1 of the specification, Applicants should insert "This application claims the benefit of priority to U.S. provisional application No. 60/006,627, filed 11/13/95, and to PCT/US96/04407, filed 3/28/96".

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 37, 38, and 55-68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 37, 38, and 55-68 are rendered vague and indefinite by the phrase "immunologically isolated stromal cells" as it is unclear if by immunologically isolated is defined as cells isolated from the organism and thus are isolated from the immune system; cells that are isolated using antibody and thus are immunologically isolated; or cells that are encapsulated such that they are not in contact with cells of the immune system. It is also unclear if these cells are *in vitro* or *in vivo*.

Claims 37 and 56 are rendered vague and indefinite for the following reasons; it is unclear what is meant by beneficial protein as the term "beneficial" is a relative term, i.e., is the protein beneficial for a host cell or a host organism, what are the benefits of such a protein? The metes and bounds of a "beneficial protein" are unclear.

Claims 37, 38, and 57 are rendered vague and indefinite by the phrase "said stromal cells" as there is no previous recitation of "stromal cells", only "immunologically isolated stromal cells". The phrase "said stromal cells" lacks proper antecedent basis. Applicants should amend the phrase to "said immunologically isolated stromal cells" or to "the cells" to overcome this rejection.

Claim 56 is rendered vague and indefinite by the phrase "an obesity factor" as it is unclear if the obesity factor is leptin or some other obesity-related protein. Clarification of "obesity factor" is requested.

Claims 58 and 65-68 are rendered vague and indefinite by the phrase "said cells" as there is no previous recitation of "cells", only "immunologically isolated stromal cells". The phrase "said cells" lacks proper antecedent basis. Applicants should amend the phrase to "said immunologically isolated stromal cells" or to "the cells" to overcome this rejection.

Claim 58 is further rendered vague and indefinite by the phrase "matched donor stromal cells" as it is unclear to what the donor stromal cells are matched.

Claim 62 is rendered vague and indefinite by the phrase "a second gene" as it is unclear which genes are encompassed in "a second gene" and it is unclear how the construct is structured, i.e., is the second gene in tandem with the first gene?, is the second gene flanked by regulatory

elements which are distinct from the first gene? The metes and bounds of the phrase "a second gene" are unclear.

Claim 59 is confusing because the claim indicates that only one regulatory element is required for the construct, yet the specification discloses that "the regulatory elements necessary for gene expression include: a promoter, an initiation codon, a stop codon, and a polyadenylation signal. It is necessary that these elements be operable in the stromal cells or in cells that arise from the stromal cells after infusion into an individual" (see page 17, lines 27-31). Is the construct containing only one regulatory element expressible?

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 37, 38, 55, and 57-68 are rejected under 35 U.S.C. 102(e) as being anticipated by Cerami *et al.* (U.S. Patent No. 5,846,796, 12/8/98, effective filing date, 2/26/93).

The claims are directed to immunologically isolated stromal cells that comprise a gene construct which contains a nucleotide sequence encoding a beneficial protein and wherein the gene construct is operably linked to regulatory elements which function in said stromal cell.

Cerami *et al.* disclose a population of isolated mesenchymal cells, i.e. cells which are removed from the body which renders the cells necessarily isolated from the immune system and

are thus immunologically isolated. The cells can be subjected to long term or short term *in vitro* culture conditions, and the cells can be genetically modified by introducing a construct comprising a nucleic acid sequence encoding a beneficial protein, wherein the nucleic acid sequence is operably linked to regulatory sequences (see, e.g., column 6, lines 65-67, column 7, lines 1-67, and Claim 1). For the introduction of exogenous genes into the cultured mesenchymal cells, any cloned gene may be transferred using conventional techniques, including, but not limited to, microinjection, transfection and transduction (see, e.g., column 6, lines 25-67). Expression vectors containing viral origins of replication can be used for gene transfer, or the mesenchymal cells can be transformed with a cDNA controlled by appropriate expression control elements such as promoters, enhancers, transcription terminators, polyadenylation sites, etc., and a selectable marker. The selectable marker can be herpes simplex virus thymidine kinase, hypoxanthine-guanine phosphoribosyltransferase, adenine phosphoribosyltransferase, dhfr, which confers resistance to methotrexate, gpt, which confers resistance to mycophenolic acid, neo, which confers resistance to G-418, etc. (see, e.g., column 7, lines 1-67 and column 8, lines 1-2). Thus, Cerami *et al.* disclose the claimed immunogenically isolated stromal cells which can be maintained in short term or long term cultures, which contain a gene construct comprising a nucleic acid encoding a beneficial protein, wherein the nucleic acid is operably linked to appropriate regulatory sequences, wherein the gene transfer can be accomplished by conventional techniques, wherein the regulatory elements include promoters, enhancers, transcription terminators, polyadenylation sites, etc., and wherein the construct contain a second gene, wherein the second gene encodes a selectable marker which can be an antibiotic resistance gene.

Thus, the disclosure of Cerami *et al.* anticipates the claimed invention.

Claims 37, 57-60, and 65-68 are rejected under 35 U.S.C. 102(b) as being anticipated by Carter *et al.* (Blood, 79:356-364, 1992).

Carter *et al.* disclose a population of isolated stromal cells, i.e. cells which are removed from the body (which renders the cells necessarily isolated from the immune system and are thus

immunologically isolated). The cells are subjected to culturing, *in vitro*, for up to 21 days. The cells contain a gene construct comprising the neo retroviral vector, which was introduced into the cells by recombinant viral vector transfer (see page 357 under "Preparation of viral supernatants" and "Gene transfer into canine LTMC"). In addition, the cells are cultured for up to 21 days (see page 357, under "Gene transfer into canine LTMC").

Thus, the cells disclosed by Carter *et al.* anticipate the claimed cells.

Claims 37, 58-61, and 65-68 are rejected under 35 U.S.C. 102(a) as being anticipated by Pereira *et al.* (Proc. Natl. Acad. Sci. USA, 92:4857-4861, 1995).

Pereira *et al.* disclose a population of isolated stromal cells, i.e. cells which are removed from the body (which renders the cells necessarily isolated from the immune system) and are thus immunologically isolated. The cells comprise a gene construct comprising the COL1A1 mini-gene which comprises the COL1A1 promoter, the human collagen I polyadenylation signal, and a beneficial protein, i.e., collagen. The cells are cultured for 4 hours, non-adherent cells are removed, and the adherent cells are further cultured for 7-10 days (see page 4857, under the section entitled "Preparation of Donor Cells", and page 4858, under the section entitled "Assays for the Marker Gene in Donor Cells").

Thus the disclosure of Pereira *et al.* anticipate the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 37, 38, 55, and 57-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carter *et al.* (Blood, 79:356-364, 1992) or alternatively over Cerami et al, taken with Ala-Kokko *et al.* (J. Biol. Chem., 266:14175-14178, 1991), Mardon *et al.* (Cell and Tissue Research, 250:157-165, 1987), Beresford *et al.* (J. Cell Science, 102:341-351, 1992), and Flier (Cell, 80:15-18, 1995).

Carter *et al.* disclose a population of isolated stromal cells, i.e. cells which are removed from the body (which renders the cells necessarily isolated from the immune system and are thus immunologically isolated) as discussed in the 35 U.S.C. 102(b) rejection above.

Alternatively, Cerami *et al.* disclose a population of isolated mesenchymal cells comprising a gene construct operably linked to regulatory elements which function in the mesenchymal cells as discussed in the 102(e) rejection above.

The above references do not disclose all of the claim-designated promoters and polyadenylation signals, microencapsulation of the stromal cells, or "donor matched cells". However, Ala-Kokko *et al.* disclose constructs containing the promoter of the human COL1A1 gene and the polyadenylation signal of human collagen II which are expressed in transfected mouse NIH 3T3 cells (see page 14175, under "Gene Constructs", and Figures 1-4). Moreover, Mardon *et al.* disclose that diffusion chambers containing adult rat bone marrow cells implanted intraperitoneally into rat hosts results in the synthesis of collagen types I, II, III, and IV (see page 158 under "In vivo culture in diffusion chambers", and Table 2). Inasmuch as these cells are

capable of expressing collagen types I-IV, one of ordinary skill in the art would have had a high expectation of successfully expressing gene constructs comprising the regulatory elements of collagen type I, II, III, or IV in stromal cells transfected or transduced with the constructs. Moreover, one of ordinary skill in the art would have been motivated to transfect or transduce the cells, by conventional methods, with constructs containing the various claim-designated promoters and polyadenylation signals, such as those disclosed by Ala-Kokko *et al.*, to determine the effect of these regulatory elements on the expression of a desired gene during the differentiation of the stromal cells into various tissues such as bone, cartilage, and fibrous tissue, as disclosed by Mardon *et al.*

The above references do not disclose that the "beneficial protein" is obesity factor, which is interpreted as leptin which is encoded by the ob gene. However, Beresford *et al.* disclose that rat marrow stromal cell cultures are capable of differentiating into adipocytic and osteogenic cells, and further, are capable of expressing collagens type I, III, and IV. The relative amounts of cells which differentiate into adipocytes and osteogenic cells, as well as the relative types and amounts of collagens synthesized by these cells is dependent on the culture conditions of the stromal cells (see page 344-345, under "Collagen synthesis", and page 348, left column, second full paragraph). As the ob gene is expressed in adipocytes (see, e.g., Flier), one of ordinary skill in the art would have been motivated to generate a construct containing the ob gene, operatively linked to regulatory elements associated with collagens type I, III, and IV for the purpose of determining the effect of these regulatory elements on the expression of the ob gene, and the effect of the ob gene in stromal cells during differentiation into adipocytes or osteogenic cells.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the stromal cells of Carter *et al.* or Cerami *et al.* by introducing into the cells constructs comprising desired genes, such as those disclosed by Carter *et al.* or Cerami *et al.* operatively linked to regulatory elements such as those disclosed by Cerami *et al.* or Ala-Kokko *et al.* to determine the relative expression of the genes under the control of these regulatory elements as the stromal cells differentiate into a variety of cell types including

chondrocytes, osteoblasts, and adipocytes as disclosed by Mardon *et al.* and Beresford *et al.* In addition, in view of the disclosure of Flier that adipocytes express the ob gene, it would have been obvious to one of ordinary skill in the art to alter the constructs of Ala-Kokko *et al.*, by replacing the polynucleotide sequence encoding the collagen gene with the polynucleotide sequence encoding the ob gene to determine the effect of the expression of the ob gene on the differentiation of stromal cells into adipocytes, chondrocytes, or osteogenic cells. As transfecting cells with various gene constructs are well known in the art, one of ordinary skill in the art would have had a high expectation of successfully making the claim-designated constructs, transfecting the stromal cells with the constructs, and expressing the genes of interest during differentiation of the stromal cells without undue experimentation absent evidence to the contrary.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear, and convincing evidence to the contrary.

No claims are allowed.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet M. Kerr whose telephone number is (703) 305-4055. Should the examiner be unavailable, inquiries should be directed to Brian Stanton, Supervisory Primary Examiner of Art Unit 1633, at (703) 308-2801. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 305-7401. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633.

Janet M. Kerr, Ph.D.
Patent Examiner
Group 1600

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